PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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20 OCT 2005
Patent department

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	18.10.2005
Applicant's or agent's file reference PRD2108-PCTf	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2004/052029	03.09.2004	12.09.2003

Applicant
JANSSEN PHARMACEUTICA N.V. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference PRD2108-PCTf	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/EP2004/052029	International filing date *(day/month/year)* 03.09.2004	Priority date *(day/month/year)* 12.09.2003
International Patent Classification (IPC) or national classification and IPC C07K14/705, G01N33/94, C12N5/10, C07D471/00, C07D513/00		
Applicant JANSSEN PHARMACEUTICA N.V. et al.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 13 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
19.05.2005	18.10.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Valcarcel, R Telephone No. +49 89 2399-2368

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2004/052029

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-30 as originally filed

Sequence listings part of the description, Pages

31-33 as originally filed

Claims, Numbers

1-29 as originally filed

Drawings, Sheets

1/5-5/5 as originally filed

☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☒ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	26-29
	No:	Claims	1-25
Inventive step (IS)	Yes:	Claims	NONE
	No:	Claims	1-29
Industrial applicability (IA)	Yes:	Claims	1-29
	No:	Claims	NONE

2. Citations and explanations (Rule 70.7):

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☒ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☐ filed together with the international application in computer readable form

   ☒ furnished subsequently to this Authority for the purposes of search and/or examination

   ☒ received by this Authority as an amendment on

2. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

1. The document numbering corresponds to the order of citation in the search report.

Re Item IV

2. The application lacks unity contradicting Rule 13 PCT. Rule 13 PCT states that for unity of invention to be present, all subject-matter should be linked by a single general inventive concept. Rule 13.2 PCT stipulates that where a group of inventions is claimed, the requirement of unity shall be fulfilled only where there is a technical relationship among those inventions involving one or more of the same or corresponding special technical features. "Special" technical features are those features that define a contribution which each of the inventions makes over the prior art.

   There is no common concept linking the different subjects claimed in the present application. There is no common technical feature between an heterocyclic compound and a $GABA_B$ receptor.

   It is noted that subject 2 (claims 25-29) relates to the compounds having formula I and the use of said compounds in the manufacture of a medicament. Said formula I comprises compounds identified as $GABA_B$ agonists using methods described in the present application. However, there is no common structural feature between the two entities. Furthermore, at least some of the compounds of formula I could not be able to bind GABA receptors or could be ligands for other kind of receptors.

   But even if it would be considered that the compounds of claims 25-29 of the present application could only bind to GABAB receptors, subjects 1 and 2 would not be unitarily linked. According to said interpretation, the common concept linking the two different subjects claimed in the present application would be the involvement of GABAB receptors. This concept is not novel, as it was disclosed in any of D1 to D19. For example D1, D2, D5, D6, D8, or D9 disclose the characterization of (and/or methods of identification of) agonists/antagonists binding to heterodimeric GABA receptors stably expressed in mammalian cells (see abstracts of said documents).

   Since no other feature could be identified neither in the description nor in the claims that could be considered a "special" technical feature in the sense of Rule 13.2 PCT,

each subject must be regarded as a separate potential invention.

Regarding subjects 1.1 to 1.3 although there is lack of unity, the International Searching Authority decided to carry out the search for one fee.

Regarding the second potential invention, a complete search could be performed with relatively little effort. Due to the lack of common technical features independent searches had to be carried out for each of the two inventions. The Applicant was invited to pay an additional search fee.

3. The Applicant elected to pay an additional fee to obtain an International search report covering also the second invention. Thus, the subject-matter of all claims (1-29) has been searched.

Re Item V

Invention 1

Articles 5 and 6 PCT

4. It is noted that in the claims 8, 12 and 18 reference is made CGP542626. Said name is unknown and absent in the description and thus as such unclear. Since in description reference is made to CGP54626 (as being a known antagonist), it has been assumed that this is a typing error and than CGP54626 was referred to.

5. **Claims 1-8, 13-18, and 21-24 contravene the Articles 5 and 6 PCT requirements.** Present claim 1 (and claims referring to it) relate to products defined by reference to a desirable characteristic or property, namely receptors in that the GABAB receptor has a high affinity binding site and a low affinity agonist binding site. There is neither support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for a GABA receptor having two agonist binding sites. The result shown in Table 2 appears to be consistent with two species binding to a given agonist, one species being homodimers and the other heterodimers.

Second, even if it would be assumed that the heterodimer expressed in the particular CHO cell line would have the claimed property, the claims (with the exception of claim

3) are not restricted to said heterodimer expressed in a particular cell line but cover all receptors having the above referred characteristic or property.

6. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the product by reference to a result to be achieved, without indicating the technical features necessary for achieving said effect. Furthermore the expressions **"high affinity binding site"** and **"low affinity binding site"** are themselves **unclear**. Without a precise definition of what high and low mean, the claims are vaguely defined.

Novelty

7. The present application does not satisfy the criterion set forth in Article 33(2) PCT because **the subject-matter of claims 1 to 24** is not new in respect of prior art as defined in the regulations (Rule 64 PCT), see the reasons below.

Prior art documents

D1 to D4 and D6 disclose CHO cell lines expressing functional GABAB receptors comprising GAGABR1a and GABABR2 subunits. The affinities of different agonists and antagonists and the potency of said ligands was studied in the same assays as in the present application. Some ligands had higher and others lower affinity.

D5: SEQ 23 of D1 is 99,9% identical to SEQ 1 of the present application (4 nts being different, at positions 63, 380, 804, and 2367);
- SEQ 22 is 99,7 % identical to SEQ 2 of the present application (aas 21 and 127 are different and there is one insertion at aa 857 in SEQ 22 of D1).
- Nts 293-3115 of SEQ 1 (GABABR1a) are 100% identical to SEQ 3 of the present application
- The protein encoded by SEQ 1 of D1 is identical to SEQ 4 of the present application. The two subunits were expressed in different cells (see pages 5-7), including CHO cells (see page 7, and figure 12), and formed a functional heterodimer which was activated by GABA receptor agonists (e.g GABA, gabapentin, see pages 6-7). Different kinds of assays to find/study agonists and antagonists are disclosed.

D7: - Nts 235-3120 of the GABABr1a sequence of Figs 6A and 6B of D3 show

99,931% identity to SEQ ID NO: 1 of the present application (2 nts differences at nts 16 and 804).
- The protein of Figure 6C of D3 is 100% identical to SEQ 2 of the pres application. - Nts. 293-3115 of SEQ ID NO: 9 of D3 (shown in Figures 10A and 10B) are 100% identical to Nts 1-2823 of SEQ ID NO: 3 of the present application. Thus SEQ 9 comprises the same cDNA as SEQ 3 of the present application.
- Accordingly protein of Figure 10C of D3 is 100% identical to SEQ 4 of PA.
On pages 33 and 52 of D3 CHO cells are disclosed as possible host cells.

D8 discloses the functional characterisation of GABAbR1a and GABAbr2 expressed in tsA cells. Several agonists were tested (see figure 3) and the rank order is disclosed to be in agreement with studies using tissue pharmacology or receptor binding (see page 1373, right column, lines 7 and 8). Thus it is assumed that the heterodimers would have a high affinity binding site and also a low affinity binding site for at least certain agonists.

D9:- SEQ 2 of D9 is 99,931% identical to SEQ 1 of the PA (GABAR1a). There are 2 different nucleotides at positions 804 and 2475.
- The GABABR1a protein (SEQ ID NO: 7) of D5 is 100% identical to SEQ 2 of the present application.
- also a GABABR2 is disclosed in D5 (figure 1, SEq ID NO: 1) which is identical to SEQ 3 of the PA, which the exception of nt 3 which was not properly sequenced (identified as N) in WO9951636 (assumed to be the same).
- The GABABR2 protein of D5 comprises SEQ 4 of the present application with the exception of aa 13, not sequenced X (N in cDNA).The one of D5 is 2 aa longer.

D10:- SEQ 48 of D6 is 99,965% identical to SEQ 1 of the present application, only 1 nt different, at position 84.
- SEQ 49 of D6 is 100% identical to SEQ 2 of PA.
Expression of the heterodimers is claimed (e.g. claim 30) as well as screening methods (see e.g. claims 31 and 32).

D11: Nts 291-3115 are 100% identical to SEQ 3 of PA. Thus HG20 is GABAr2. GABABR1a is also disclosed and is 99,8% identical at the DNA and protein level to

GABABR1a of the present application.
D11 further discloses that heterodimers of GABABR1a and GABABr2 are functional and are bound an activated by different agonists (see e.g example 12, or claim 16). CHO cells are disclosed at different sections as suitable to express GABA receptors (see e.g. pages 32, 40, 44, 48, 55, 57, and 57).

D12 discloses expression of GABA receptors in oocytes and HEK293T cells (also functional GABABr1a and GABABr2 heterodimers). At least the GABABR2 is identical to that of the present application. Also assays to identify agonists are disclosed.

D13 discloses a cDNA encoding GABABr2 is 99,9% identical to SEQ 3. The protein is 100% identical to SEQ 4 of the present application. Also heterodimres disclosed (see e.g claims 58 and 58), or paragraph 0481). Also the use of CHO cells for expression said proteins is disclosed, see e.g. claims 96, 111, 119, 141, and 170.

D14 discloses a GABAR1a protein identical to SEQ 2 of the present application (as cited in te description of the present application).

D15 discloses a GABAR2 identical to SEQ 4 of the present application (as cited in te description of the present application).

D17 to D19 disclose CHO cell lines expression GABABR1b and GABABR2 subunits, and the binding of the GABAB receptors to different agonists and antagonists, including the allosteric modulation of certain ligands (see e.g. D19).

7.1 The GABAB receptor proteins are defined in claim 3 in terms of a process of manufacture. For the assesment of the present claim on the question of whether or not they fulfil the requirements of novelty, no unified criteria exist in the PCT. The patentability can also be dependent upon the formulation of the claim. The EPO, for example, does not recognize a product as novel merely by the fact that it is produced by means of a new process.

The IPEA has considered that as far as the GABA receptor is not demonstrated to be

different to these GABA receptors formed by the GABABR1a and GABABR2 subunits expressed in the prior art in CHO cells (e.g. in D1 to D4, and D6), this claim is considered as not novel. Accordingly, also claims 1 and 2 are considered as not novel (they are broader than claim 3).

Furthermore, if a new property is discovered for a known protein, inclusion of said feature in a claim directed to the protein does not render the claim novel, since this is an intrinsic property of the protein.

7.2 The same applies for the deposited cell line. Deposition a cell line does not render said cell line novel.

The IPEA can not find any feature having support in the application as filed wich distinguishes the particular CHO line expressing the same subunits of the present application. Thus, even the cell line (claim 5) has to be considered as not novel.

7.3 It is noted that the cDNA sequence of SEQ ID NO: 1 has at least 1 nt difference to known human GABAbR1a cDNAs. However, in view of the fact that the protein encoded is identical to that of SEQ ID NO: 2 of the present application, and that other cDNAs having either 1 or 2 nts differences coded for the same GABABR1a protein (see any of D5, or D6 to D12), it is assumed to be the same cDNA, and the nt differences, eg. at nucleotide at position 804 of SEQ ID NO: 1 to be the result of a sequencing mistake.

In case the Applicant can demonstrate that said nucleotide is a mutation, said cDNA would be considered as novel. Said, mutation would not however be considered as inventive as long as this mutation would not result in an unexpected technical effect.

Even further, claim 2 does not refer to the nucleotide sequence having SEQ ID NO: 1, but to the protein encoded by it which is not novel (see below).

7.4 It is standard in the art the use of recombinant GABAB receptors in methods to identify agonists and antagonists (see any of D1 to D19). The ISA is unable to find any feature in the method claims which distinguishes said methods from the standard

methods involving recombinant GABAB receptors. Thus, the subject-matter of claims 4, and 6-24 is considered as not novel.

Inventive step

8. It is again noted that even if the particular cell line could be clearly defined and demonstrated to be novel, inventive step could be only recognized if said cell line would show any unexpected effect.

The same applies for the particular SEQ ID NO: 1. Even if it turns out to be a novel GABABR1a mutation (and not the result o a sequencing mistake), then said particular sequence could be considered inventive if a particular effect is associated to it.

INVENTION 2

Novelty

9. The present application does not meet the criteria of Article 33(1) PCT, because **the subject-matter of claim 25 is not new** in the sense of Article 33(2) PCT.

D20 to D22 and D24 disclose compounds of formula I with Z1-Z4 as defined in section (c) of claim 25 of the present application (see e.g, page 1 of D20, compound I; page 1 of D21, compound I; or page 1 of D22, compound I; or compounds of column 9 of SU 811776, referred to in D24). These compounds are disclosed to have the following pharmacological activities:
- in D20, neurotropic, analgesic, inflammation-inhibiting, antipyretic, and antihypoxic activities (see abstract);
- in D21, neurotropic and antidepressant activities (see abstract);
- in D22, psychotropic, especially antidepressant and tranquillizing activities (see abstract).
- in D24, possible medicinal applications (see "USE" section of the abstract.

Claim 25 of the present application refers to the use of the recited compounds for the manufacture of medicament for the treatment of an indication **such as** one of the 6 particular indications recited. The expression "such as" is in no way limiting the scope of the claim. The ISA considers that the use of any of the compounds falling under the scope of formula I as defined in claim 25 for the preparation of a medicament for

any kind of disease falls under the scope of claim 25.

Inventive step

10. The present application does not meet the criteria of Article 33(1) PCT, because **the subject-matter of claims 26-29 does not involve an inventive step** in the sense of Article 33(3) PCT.

The compounds referred to in claim 27 of the present application appear to be novel. Said compounds are disclosed in the present application to be $GABA_B$ receptor agonists (see from line 31 of page 15 to line 5 of page 19).

On Table 2 (page 28) of the present application 4 examples falling under the definition of claim 27 of the present application are shown to have comparable binding (3H-GABA binding) and signal transduction (GTPγS binding) properties than baclofen and GABA.

D25 (considered as the closest prior art) discloses the effects of GABA, baclofen and other $GABA_B$ receptor agonists in reducing transient lower esophageal sphincter relaxations (see e.g. Table 1 on page 13, or claims 1-10).

In view of D25, the technical problem would have been to provide alternative $GABA_B$ receptor agonists. The solutions disclosed in the present application are the compounds defined in claim 27. It appears at present that the compounds referred to in claim 27 are mere alternatives to GABA an baclofen, or the other $GABA_B$ receptor agonists disclosed in D25.

An arbitrary choice from a collection of possible solutions cannot involve an inventive step, because, in order to be patentable, the selection must not be arbitrary but must be justified by the technical purpose, i.e. by a hitherto unknown or unexpected technical effect which is caused by those features distinguishing the claimed $GABA_B$ receptor agonists from the ones of the prior art.

In the absence of any unexpected effect as compared to the $GABA_B$ receptor agonists of D25, the compounds of claim 27 are considered not to involve an

inventive step.

10.1 Even further, in case certain compounds falling under the scope of claim 27 would display an unexpected effect as compared to the $GABA_B$ receptor agonists of D25, only a claim limited to the compounds having said effect could be considered inventive.

10.2 Dependent claims 26 and 28-29 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of inventive step, the reasons being the same as for claim 27: lack of an unexpected effect over the $GABA_B$ receptor agonists of D25.